

## **REMARKS**

### **Introductory Comments**

Claims 1-16 are pending. The Examiner has rejected all pending claims.

The Examiner has rejected claims 1 and 15 under 35 U.S.C. §112, first paragraph, alleging that the specification does not reasonably provide enablement for making a vaccine.

The Examiner has rejected claims 1-16 under 35 U.S.C. §103(a), alleging that the claims are unpatentable over Milagres *et al.* (1996) FEMS Immun Med Microbiol 13: 9-17 in view of Lieberman *et al.* (1996) JAMA 275: 1499-1503.

These rejections are traversed and believed to be overcome for reasons discussed below.

Applicants acknowledge with appreciation the withdrawal of the rejection of the claims under 35 U.S.C. §102(b).

### **Overview of the Amendments**

Claim 15 has been canceled. The cancellation of claim 15 is without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to pursue the subject matter of the canceled claim in another application.

### **Addressing the Examiner's Objections and Rejections**

#### **1. Rejection of Claims 1 and 15 under 35 U.S.C. §112, First Paragraph**

The Examiner has rejected claims 1 and 15 under 35 U.S.C. §112, first paragraph, asserting that the specification does not reasonably provide enablement for making a "vaccine." The rejection is made moot by the cancellation of claim 15. The Examiner is respectfully requested to withdraw this rejection.

#### **2. The Rejection of Claims 1-16 Under 35 U.S.C. §103(a)**

The Examiner has rejected claims 1-16 under 35 U.S.C. §103(a), asserting that the claims are unpatentable over Milagres *et al.* in view of Lieberman *et al.* The Examiner stated that Milagres *et al.* teach an immunogenic composition comprising NmB and NmC, and Lieberman *et al.* teach an Nm oligonucleotide-protein conjugate where the carrier is CRM<sub>197</sub>. The Examiner reasons that it would have been obvious to combine an oligosaccharide conjugated to a carrier with an outer membrane protein.

The applicants traverse the rejection. In order to render claims obvious, the burden is on the Office to establish a *prima facie* case of obviousness for which three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references. Second, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all the claim limitations. The teachings or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The cited references do not teach or suggest all the claim limitations of the invention, and the applicants submit that the cited combination is based on impermissible hindsight reconstruction as there is no motivation to combine the references. Therefore, the Examiner has not established a *prima facie* case of obviousness.

The present invention relates to a composition that induces an immune response to two serogroups of *Neisseria meningitidis*. The immunogenic composition comprises an NmC (*Neisseria meningitidis* C) oligosaccharide conjugated to a first carrier and NmB (*Neisseria meningitidis* B) outer membrane protein. The present invention thus relates to combination immunogenic compositions and methods for inducing an immunological response to *Neisseria meningitidis* B and C.

Milagres *et al.* and Lieberman *et al.*, when taken together, do not teach or suggest NmC oligosaccharide conjugated to a first carrier. In Milagres *et al.*, Swiss mice were immunized with a purified capsular polysaccharide from NmC and an outer membrane vesicle (OMV) extracted from NmC or NmB strains (page 10, last paragraph of the Introduction and page 11, column two). Neither of Milagres' NmC vaccine

components are analogous to applicants' NmC oligosaccharides. Particularly, as explained at page 4, lines 4-9 of the application, the NmC oligosaccharides used by applicants are fragments including about 12 to 22 repeating units. Neither the NmC polysaccharide or the NmC OMV used by Milagres represent such fragments. Moreover, the vaccines used Miagres did not use any carriers.

Lieberman *et al.* does not supply the missing links. Lieberman uses a combined NmA and NmC oligosaccharide-protein conjugate vaccine. The vaccine composition was obtained by mixing 48.7 µg of CRM<sub>197</sub> (a mutant diphtheria toxin), 11.15 µg of NmA oligosaccharide and 11.7 µg of NmC oligosaccharide with 1 µg of aluminum hydroxide (page 1500, middle column, under the title Vaccines). The diphtheria toxin is thus admixed with the oligosaccharides from two meningitidis strains. Although the protein might become associated with both of the oligosaccharides, it certainly is not conjugated to NmC. Furthermore, Liberman nowhere discloses the use of an NmB immunogen in combination with an NmC oligosaccharide.

Moreover, the ratio of oligosaccharide to CRM<sub>197</sub> employed by Lieberman *et al.* falls outside the oligosaccharide to protein ratio disclosed in the present application. The reference discloses NmC and CRM<sub>197</sub> present at a ratio of 0.24, whereas the applicants disclose, at page 4, lines 13-15, maintaining the oligonsaccharide to protein ratio at from about 0.3 to about 0.8.

Based on the foregoing, it is evident that the references do not suggest or provide the motivation to provide an immunogenic composition as claimed. The particularity needed to establish a motivation to combine references was discussed in *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002). In *In re Lee*, the Board determined that it was not necessary to present a source of a teaching, suggestion, or motivation to combine the references because the conclusion of obviousness may be made from common knowledge and common sense of a person of ordinary skill in the art. The court reversed the Board's decision in sustaining a rejection under 35 U.S.C. 103 and stated: "The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent ... cannot be dispensed with. The need for specificity pervades this authority." The Federal Circuit further stated that omitting the

need for a specific suggestion in a particular reference to support the motivation to combine was both a legal error and arbitrary agency action (at 1434). Thus, the motivation to combine must be found in the references themselves, and the requirement is a critical safeguard against hindsight reconstruction to arrive at the applicants' invention.

In the present case, the Examiner has not met the required specificity to establish a motivation to combine the references. The Examiner has identified references which, at best, individually disclose various components of applicants' invention. However, the identification of each claimed element in prior art is not sufficient to negate patentability as the Examiner is required to show, with evidence and detailed reasoning, that the motivation to combine can be found within the references cited. This the has failed to do. Accordingly, a *prima facie* case of obviousness has not been established.

The combination of the cited references does not provide or suggest all the elements of the pending claims, and the combinations are based on impermissible hindsight reconstruction. Therefore, the Examiner has not established a *prima facie* case of obviousness, and the Examiner is respectfully requested to withdraw this rejection.

### CONCLUSION

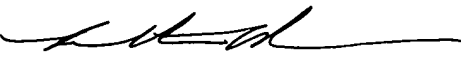
Applicants respectfully submit that the claims define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please send all further written communications in this case to:

Alisa A. Harbin, Esq.  
CHIRON CORPORATION  
Intellectual Property - R440  
P.O. Box 8097  
Emeryville, CA 94662-8097.

Respectfully submitted,

Date: 12/10/02

By:   
Roberta L. Robins  
Registration No. 33,208  
Attorney for Applicants

CHIRON CORPORATION  
Intellectual Property - R440  
P.O. Box 8097  
Emeryville, CA 94662-8097  
Telephone: 650-325-7812  
Facsimile: 650-325-7823

APPENDIX A

Marked up Version of The Claims.

Claim 15 has been canceled.